7. PROTOCOL DEVIATION REPORTING

7.1 Background

DCP, as a protocol sponsor, is responsible for implementing and maintaining quality assurance/quality control SOPs to ensure that studies are conducted according to the protocol (compliance), good clinical practice (GCP), and all applicable regulatory and DCP requirements. A protocol deviation is any noncompliance with the protocol, GCP, regulatory standards, or DCP requirements. The noncompliance may be on the part of the participant, the investigator, or the study site staff. The term "deviation" is not to be confused with the term "deficiency." The term deficiency is used by the CRA to assess site performance at a monitoring visit.

It is the responsibility of the site staff to identify deviations as they occur and to report them to the DCP Medical Monitor. Corrective actions are developed by the site and implemented promptly. These practices are consistent with Good Clinical Practice §4.5.1, §4.5.2, §4.5.3, §5.1.1, §5.20.1, and §5.20.2.

The relationship of deviation reporting to monitoring visits is that frequently the CRA identifies deviations during a study site monitoring visit. If this occurs, the CRA will instruct the study site staff to report the deviation to the Medical Monitor and the local IRB. While deviations may be discovered during a site visit, sites should not rely on the monitoring visit alone to identify and report deviations. It remains the responsibility of the site to use continuous vigilance in the detection and reporting of deviations to DCP as soon as they occur.

7.2 Purpose

The identification and reporting of deviations critically affects both the conduct and analysis of a clinical trial. For example, a consistent pattern of a particular deviation may reveal the need to amend the protocol to improve participant compliance. Numerous deviations related to the collection of safety data may affect the analysis of study data. Recognizing trends and patterns of deviations allows the PI to correct operational issues and to perform continuous quality improvement.

Standardizing the process of detecting and reporting deviations will promote the following outcomes:

- Early identification of deviation trends that require corrective action by the study site staff;
- Rapid correction of protocol problems (when appropriate) in response to deviation trends;
- Prompt (i.e., real time) reporting by site staff of protocol deviations;
- More accurate statistical analysis of the protocol outcomes with integration of deviations data;
- Consistent followup of corrective action to evaluate effectiveness;
- Consistent expectations for monitoring DCP-sponsored protocols for compliance;
- Identification of study site staff educational needs; and
- Performance data for annual site contract evaluation.

7.3 Procedure

The expected outcome is that the study site staff are knowledgeable about the protocol and follow the protocol as outlined. If the study staff have questions about the protocol, the PI, DCP Medical Monitor, or nurse specialist should be consulted. (Check Appendix A for the telephone and fax numbers and email addresses of the DCP staff.)

- When a protocol deviation is identified, the PI, or designee:
  - Documents the deviation and specifies the sections of the protocol related to the deviation, using the Protocol Deviation Notification Form in Appendix D;
  - Describes corrective action taken to minimize the risk of a repeat occurrence of the deviation;
  - Signs the completed Protocol Deviation Notification Form; and
  - Faxes the completed Protocol Deviation Notification Form to the DCP Medical Monitor. See Appendix A for a list of staff.

- Upon receipt of the Protocol Deviation Notification Form, the Medical Monitor or designee will:

  - Confirm the deviation is a bona fide protocol deviation;

  - Review the corrective action plan and determine if the plan is acceptable or requires additional action plans. If additional action plans are required, work with the PI or designee to ensure that appropriate corrective action plans are developed and implemented;

  - Sign the Protocol Deviation Notification Form;

  - Fax the Protocol Deviation Notification Form to Westat (see Appendix A); and

  - Follow up with site staff to ensure that the corrective action plan is implemented and no other deviations of that type have occurred.

- Upon receipt of the Protocol Deviation Notification Form, the Westat Project Director will:

  - Forward a copy of the completed Protocol Deviation Notification Form to the study site with a signed cover letter.

  - Review the deviation and corrective action with the audit manager and the CRA for the site as needed. There may be collaboration with the site staff, DCP Medical Monitor, and Westat staff to resolve outstanding issues related to the action plans and/or implementation of the action plans.

  - Forward a paper copy of the completed deviation form to Westat Task 1 staff to be logged into the Deviation Database.

  - Distribute the Protocol Deviation Notification Form to CCS Associates.

  - Create standardized reports according to needs identified by DCP, such as deviation type, frequency, severity, etc.

7.4 Examples of Deviations

Deviations, or noncompliance, may result from the action of the participant, investigator, or study site staff. Frequently, noncompliance is not attributable to an error and should not be viewed as punitive in nature; it is simply an occurrence that deviates from, or does not comply with the protocol. In other situations, the deviation may be due to error and may have a more serious impact on the conduct or the outcome of the trial. Whatever the cause, repeated deviations of a similar type are particularly

important as they may signal the need for change (e.g., protocol, operations, communication). Deviations are viewed as an opportunity to make improvements and may signal the need for education.

The following are provided as samples of noncompliance with the protocol, GCP, or DCP guidelines that should be reported as deviations:

- Study assessments missed or obtained outside the visit windows as outlined in the protocol;
- Errors in dispensing the study agent (e.g., wrong dose, wrong time, wrong participant, wrong agent);
- Informed consent not obtained prior to enrollment or failure to use the correct version of the informed consent;
- Consent form missing, or consent form not signed and dated by participant;
- Consent form missing updates of information distributed as an amendment to the protocol;
- Missing CRFs or repeated missing data on CRFs;
- AE or SAE not reported according to DCP guidelines;
- Participant enrolled in a study who did not meet the eligibility criteria as specified in the protocol;
- Source documents missing or lacking intervention to support data reported on the CRF;
- Additional agent used, which is not permitted by protocol;
- Unjustified dose modifications or failure to modify doses according to protocol;
- Unjustified (and/or undocumented) delays in procedures; and
- Protocol never approved by IRB, or other IRB violations.